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Renovasculopathies of nephrosclerosis in relation to atherosclerosis at ages 25 to 54 years

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Renovasculopathies of nephrosclerosis in relation to atherosclerosis at ages 25 to 54 years. Renovasculopathies of hypertension include arteriolar hyalinization and arterial intimal fibroplasia. Atherosclerotic features of coronary arteries and aorta include fatty streaks and raised lesions. Data were obtained from a series of 573 autopsies of black and Caucasian males and females aged 25 to 54 years, who died of violent and natural causes unrelated to atherosclerosis. Analysis showed positive correlations of coronary and aortic raised lesions with arteriolar hyalinization. Arterial intimal fibroplasia correlated positively with raised lesions in the aorta but only weakly and inconsistently in the coronary arteries. The extent of fatty streaks in the coronaries, as in the aorta, did not correlate with either form of renovasculopathy. These results provide evidence that hyalinization of renal arterioles may be a marker for young people who have the most advanced coronary atherosclerosis, and who therefore have an early start upon a course toward coronary heart disease later in life.

Hypertensive subjects examined at autopsy are often found to have nephrosclerosis. This condition of the kidney is distinguished by hyalinization of arterioles and by fibroplastic intimal thickening of small arteries. In recent years, these two classes of renovasculopathy have been evaluated separately by different morphometric approaches [1–8]. Both hyalinization of arterioles and fibroplasia of arteries tend to increase with age in most visceral organs [1, 7, 9, 10]. Moreover, both features are exaggerated in the kidneys of hypertensive compared with nonhypertensive subjects. The association of hypertension with microvascular abnormalities in viscera other than the kidney has received little attention, but is usually said to be weak or absent [9, 10]. Also, diabetics tend to show especially severe renal arteriolar hyalinization, but no more fibroplastic arteriosclerosis than expected from their higher blood pressure status [1, 4, 11]. Cigarette smokers may have excessive microvascular abnormalities in the kidney and other viscera [12–14], although confirmation of this suggestion has been difficult to obtain [15].

In a previous report [16], subjects with coronary heart disease (CHD) revealed greater hyalinization of arterioles than did matched control subjects, but did not show greater arterial intimal fibroplasia. This outcome suggested a closer association of coronary artery disease with the hyaline than with the fibroplastic type of vasculopathy. The present report extends those inquiries beyond the subjects with overt CHD, and looks at the early stages of coronary artery disease in basal subjects, that is, those who died from violent or natural causes other than atherosclerosis-related conditions.

The subjects of this series who had coronary heart disease (CHD), as previously reported [16], gave results that seemed paradoxical. The type of vasculopathy which related less well to CHD, arterial fibroplasia, was repeatedly reported to be the better proxy for blood pressure [3–6]. Moreover, the two vasculopathies are usually taken to be features of the same pathological entity, nephrosclerosis, and therefore they would be expected to behave alike when correlated with other variables, such as CHD. Further exploration of these challenging results seemed in order.

Methods

Selection of cases

The Community Pathology Study (CP-Study) included 736 subjects autopsied in community hospitals and the Coroner's Office according to standardized protocol while our technical personnel assisted. Ages were restricted to 25 to 54 years, but subjects otherwise included all African American and Caucasian men and women without further selection. Cause of death was determined from autopsy findings, including objective evaluation of sliced hearts and longitudinally opened coronary arteries, as well as clinical information available at the time of autopsy. The 163 subjects with CHD and other atherosclerosis-related conditions have been addressed in a separate report [16], and were excluded from this analysis. The 573 subjects in the basal group were retained for this report. The basal group comprised those whose deaths were due to violence and to noncardiovascular diseases such as cancer, cirrhosis, and infections. Methods were essentially those previously reported [17, 18]. The omitting of atherosclerosis-related conditions was done to avoid biasing the autopsy sample with an excess of subjects that were uncommon in the living population. Since atherosclerotic lesions in basal subjects were symptomless precursors of coronary heart disease, the extent of such lesions was not likely to affect mortality or selection for autopsy, and was therefore apt to be reasonably typical of the population [17]. Moreover, the direct correlation of renovasculopathies with atherosclerosis in basal subjects could be addressed without concern for ancillary factors that precipitate heart disease and mortality.

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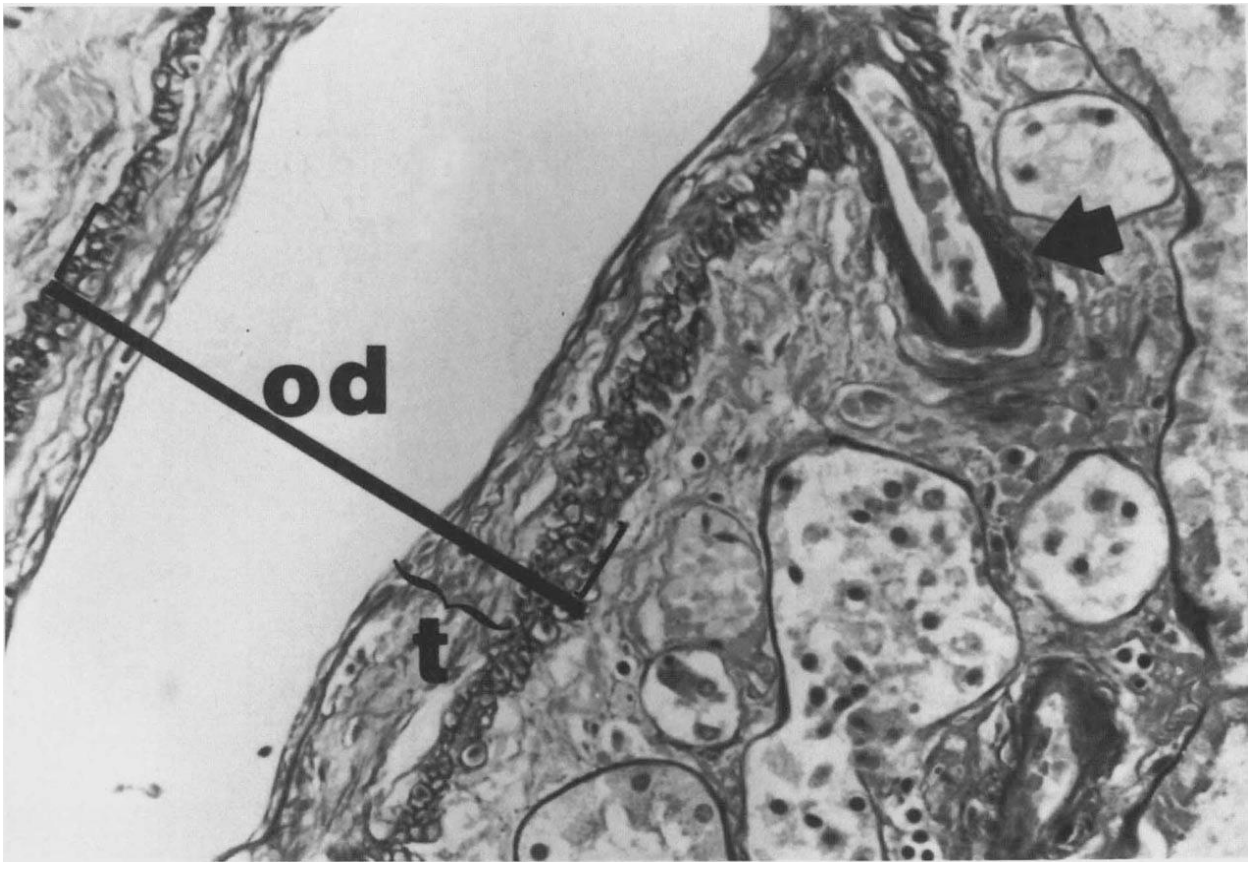

Fig. 1. *Arrow marks a hyaline deposit in an arteriole.* Ratio of intimal thickness, t, to outer diameter, od, is the pathological variable of interest, R = t/od (PAS-hematoxylin, ×400).

Processing of tissues

Samples of kidney tissue were managed as for a routine autopsy. Blocks of tissue cut perpendicularly to the capsular surface were fixed and stored in acetate-buffered 10% formaldehyde. Samples were embedded in paraplast, sectioned at 6 μ and stained with PAS-alcian blue. Generally, a total 2 to 4 cm^2 area of renal cortex was represented in one or two sections of tissue. Coronary arteries and aortas were retrieved at autopsy and managed according to previously established protocol [18]. After removal of adventitia, arteries were opened longitudinally, flattened, fixed in 10% buffered formaldehyde, stained with Sudan IV, and sealed in plastic bags.

Morphometry: Hyalinized arterioles

Cortical tissue of each kidney section was scanned systematically under the 10 × objective lens, counting all of the hyalinized vessels in accordance with previously described protocol [6]. This procedure captured some hyalinized efferent as well as afferent arterioles, and occasionally a terminal artery (Fig. 1). The area of tissue section represented by renal cortex was measured, and the counts of hyalinized arterioles per cm^2 of tissue were expressed as the square root of the counts (denoted by $\sqrt{Hy}$). The square root is taken to diminish the severe skewness in the frequency distribution; this transformation yields a nearly linear relationship of $\sqrt{Hy}$ to age.

Morphometry

Intimal fibroplasia of arteries. Up to 40 arterial profiles were examined systematically using previously reported techniques [3, 6]. The outer diameter of the least axis of the elliptic profile was measured under the 10× objective lens, excluding the adventitia, and measuring from one outer media to the other (Fig. 1). The thickness of intima was measured under the 40× lens, also along the least axis, using the better presented of the two opposite walls (that is, lacking tangential sectioning, branch ostium, or artifact). If the two opposite walls were equally well presented, then an average of the two was used. The intima, as the percent of the outer diameter, averaged over all readings within the size range of 150 to 300 μ outer diameter (OD), is called R_c; a similar measure averaged for vessels of 80 to 150 μ outer diameter is called R_r.

Atherosclerosis. Three pathologists independently made visual estimates of the extent of intimal surface involved by fatty streaks and by raised lesions. The averages of the three readings are used in the analyses reported here. With RL and FS symbolizing the percentages of intimal surface affected by raised lesions and fatty streaks respectively, the surface at risk of having fatty streaks is 100 − RL. Using FaF to symbolize the percentage of fatty streaks found in flat surfaces, FaF = FS/(100 − RL) was calculated to give fatty streaks as a percentage of the area at risk [19]. The total surface involved with all types of lesions is ATL = FS + RL.

Statistical analysis

The statistical significance of observed differences in extent of atherosclerosis by sex, race, and quartile groupings of the age adjusted measures of the renovasculopathies, was examined through F-tests in analysis of covariance that include age as covariate. Selected correlations within 10 years age groups were tabulated. Basic statistics and descriptions of variables are given in **Appendix 1**. Backward elimination stepwise multiple regression is used in **Appendix 2** to explore the relation of age, race, sex, and our three measures of renovasculopathy, as independent variables, to the advanced lesions of atherosclerosis, as the dependent variable. The standardized regression coefficients of the independent variables retained at the end of the backward elimination process serve to assess the relative importance of the effect of each of these variables. **Appendix 3** offers a cursory comparison of this study with other studies that provide comparable data concerning some questions of interest. Standard SAS 6 (SAS Institute Inc., Cary, NC, USA) procedures — MEANS, UNIVARIATE, CORR, REG, and GLM — were used to execute the analyses as outlined.

Results

Measures of atherosclerosis by race and sex

The aortas and coronary arteries of African Americans had more extensive fatty streaking than those of Caucasians ($P < 0.01$, FaF represented in the upper parts of the bars in Fig. 2), but there was no evidence of a race difference in raised lesions (RL = lower parts of the bars). The race difference in fatty streaks of the aorta was large enough to affect the measure of all types of lesions ($P < 0.04$, ATL = full height of the bars in Fig. 2). The aortas (but not the coronary arteries) of females had more extensive fatty streaking than those of males ($P < 0.01$, Fig. 2), and this difference was also evident in the measure of all types of lesions ($P < 0.02$). The coronary arteries (but not the aortas) of males had greater involvement with raised lesions than did those of females ($P < 0.01$, Fig. 2), and although this seemed greater in Caucasians than in African Americans, the interaction effect was not significant ($P = 0.20$). (All interactions were not significant, implying that the race differences are similar in both sexes and the sex effects are similar in both races.)

Coronary lesions versus arteriolar hyalinization

Results for the coronary arteries are seen in the upper part of Figure 3. Raised lesions were most extensive in subjects with the greatest hyalinization in renal arterioles and least extensive in subjects with the lowest hyalinization scores ($P < 0.02$, RL = lower part of bars in Fig. 3). Fatty streaks did not relate significantly to hyalinization ($P = 0.16$, FaF represented in the upper part of the bars in Fig. 1). The overall extent of lesions, regardless of type (ATL), reflected chiefly the effect of raised lesions, rising significantly with increasing hyalinization ($P < 0.03$, ATL = total height of bars in Fig. 1). (Again, the interaction terms in the ANOVA were not statistically significant, implying that the effects on coronary lesions attributed to hyalinization are not modified by sex or race.)

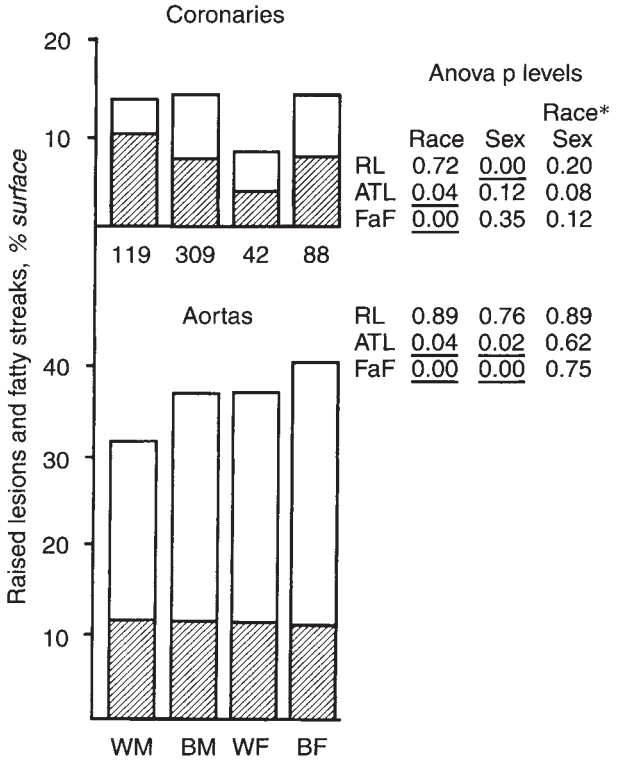

Fig. 2. *Mean extent of raised lesions (▨) and fatty streaks (□), age adjusted, are shown for white males (WM), black males (BM), white females (WF), and black females (BF).* Numbers of cases are given at the bases of the coronary artery bars. Analysis of variance results, including interactions of race*sex, are reported as *P*-levels (probability of effects occurring by chance).

Aortic lesions versus arteriolar hyalinization

Results for the aorta are depicted in the lower part of Figure 3. As for coronary arteries, raised lesions in the aorta were most extensive in the subjects with the greatest hyalinization in renal arterioles ($P < 0.00$, RL = lower part of bars in Fig. 3). Fatty streaks were not significantly related to hyalinization ($P = 0.62$, FaF represented in the upper part of the bars in Fig. 3). All types of lesions combined (ATL) failed to reflect the group differences in raised lesions ($P = 0.29$, ATL = total height of bars in Fig. 3).

Coronary lesions versus arterial intimal fibroplasia

None of the measures of atherosclerosis in the coronary arteries showed significant associations with either measure of fibroplasia, either R_r or R_c in the pool of all cases combined. For R_r, the findings are given in the upper part of Figure 4. A similar chart for R_c shows the same lack of significance as seen in Figure 4, and that redundant chart is omitted here.

Aortic lesions versus arterial intimal fibroplasia

Raised lesions in the aorta were most extensive in the subjects with the greatest fibroplasia in renal small arteries ($P < 0.00$, RL = lower part of bars in Fig. 4). Other measures of atherosclerosis in the aorta showed no significant associations with fibroplasia. (The excess of aortic raised lesions in the highest grouping interval was due almost entirely to the 12 women in the group who

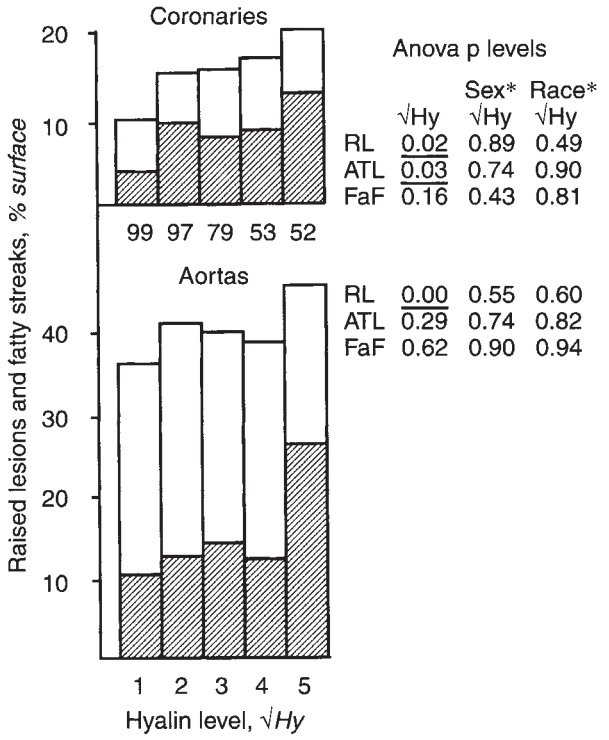

Fig. 3. *As for Figure 2, giving mean age-adjusted atherosclerosis measures for subjects grouped by hyalinization of renal arterioles [age-adjusted to age 36.2 years – cutpoints between groups are 1.0, 1.8, 2.6, 3.4 $\sqrt{(N/cm^2)}$].* Symbols are: (□) fatty streaks; (▨) raised lesions.

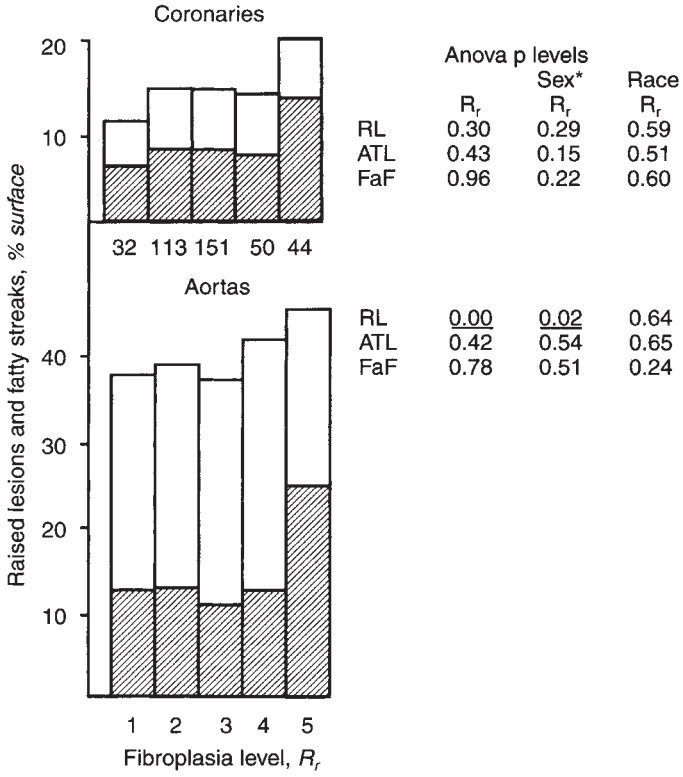

Fig. 4. *As for Figure 2, giving mean age adjusted atherosclerosis measures for subjects grouped by intimal fibroplasia of renocortical arteries (age-adjusted to age 36.2 years – cutpoints between groups are 1.3, 2.6, 3.9, and 6.2% OD).* Symbols are: (□) fatty streaks; (▨) raised lesions.

averaged 33.5% of the aortic surface affected by raised lesions, thereby generating a significant Sex*R_r interaction in Fig. 4, $P < 0.02$).

Correlations within age groups

Raised lesions in the coronary arteries and aortas are examined within 10-year age groups by computing correlation coefficients to relate these measures to some selected variables (Table 1). Of special interest is the finding that the correlation of raised lesions with hyalinization of renal arterioles is strengthened with rising age (third row of Table 1).

Table 1. Correlation coefficients relating raised lesions in the coronary arteries and aortas to selected variables by 10-year age groups

	Coronary arteries			Aorta		
Variable	25–34	35–44	45–54	25–34	35–44	45–54
R_c	0.06	0.16*	0.06	−0.05	0.27[a]	0.02
R_r	−0.04	0.11	0.11	0.05	0.26[a]	0.17
√Hy	0.06	0.14	0.33[a]	0.07	0.24[a]	0.30[a]
FaF, cor.	0.18	0.49[a]	0.47[a]	0.16[a]	0.09	−0.07
FaF, aor.	0.20[a]	0.12	−0.07	0.49[a]	0.10	0.13
N	134	158	95	135	159	98

Abbreviations are: R_c and R_r, arterial fibroplasia in the close and remote vessels, respectively; FaF, fatty streaks as a percentage of flat surfaces in the coronary arteries (cor.) and aorta (aor.); *N*, number of cases with kidney samples (numbers with arterial samples are larger than these by about 40%).

[a] $P < 0.01$

Discussion

Those studies which have examined separately the hyalinization of arterioles and the intimal fibroplasia of arteries in the renal cortex all agree that both types of lesion are significantly related to blood pressure [1–5, 8, 10, 20, 21]. A review of these reports, given in Appendix 3, suggests that fibroplasia is a better correlate of blood pressure than is hyalinization.

The present study reports that raised atherosclerotic lesions in the coronary arteries related better to renal arteriolar hyalinization than to arterial intimal fibroplasia, in this collection of basal subjects aged 25 to 54 years. This result suggests that the correlation of renovasculopathies with atherosclerosis might be mediated by other factors in addition to high blood pressure. Since fibroplasia is the better proxy for blood pressure, it is the form of vasculopathy which should relate better to arterial lesions, if the connection is due to hypertension; that outcome was not found here. Rather, it was the hyalinization of arterioles that identified those young individuals with early atherosclerotic lesions in the coronary arteries.

Two previous studies have shown that subjects dying at ages 25 to 54 years of coronary heart disease often reveal severe renocortical arteriolar hyalinization [16]. Another study has reported that fibrotic intimal thickenings, seen histologically in the coronary arteries at ages 10 to 28 years, correlate strongly with arteriolar hyalinization [22]. All of these findings, together with results reported here, suggest that hyalinization of renocortical arterioles

can be viewed as a youthful marker for future heart disease. This much neglected pathological entity merits greater general interest than is now appreciated.

An overview of what is known about renal arteriolar hyalinization can be briefly summarized. An association with diabetes mellitus is well known [1, 4, 12]. An association with smoking has been reported [13–15], but not confirmed [16]. Although the term "arteriolosclerosis" is often applied, no evidence has been forthcoming to show that the hyaline masses are hard; rather there is some reason to think that they may be soft [23]. Hyaline masses are often rich in complement fragments, especially iC3b [6, 19, 24]. The masses often contain cholesterol, phospholipid, triglyceride, tryptophan, tyrosine, and cystine/cysteine [25]. Although the presence of fibrin can be demonstrated histochemically [26], its quantity is thought to be small [24, 27–29]. Hyalinization of arterioles is characteristic of cyclosporine toxicity [30, 31]. All of these features of arteriolar hyalinization fail to apply to arterial intimal fibroplasia, which is structurally and histochemically a greatly different process. Arterial fibroplasia occurs in those mammalian species that have life spans exceeding eight years; however, hyalinization of arterioles is uniquely human, having been found, until now, in no other species [32].

The way that arteriolar hyalinization fits together with intimal fibroplasia into the pathogenesis of nephrosclerosis is not known. The simple details of histogenesis remain unknown for both types of vasculopathy. Critically important studies needed to elucidate these matters have been few and infrequent. Only two reports have given findings from studies of serial sections [11, 33], and both studies gave no data on fibroplasia, thus offering no evidence for an anatomic connection between hyalinization and fibroplasia. Electron microscopic studies have been little more than exploratory [21, 27–29, 34–36], and have shown no more than random anatomic associations between the two types of vasculopathy. Injection casts have received little attention for defining pathologic features of renal microvasculature in the human [33, 37]. Microsphere embolization of postmortem specimens has not been reported. Given such scanty information, many theories can be equally well defended. Either hyalinization or fibroplasia or both might be viewed as causes or as consequences of high blood pressure. The two processes may or may not be acting or responding independently of each other, or else they may be in some way linked together. Considerable reason exists for treating the two renovasculopathies in separate ways. Fibroplasia appears to be a local response by the cells resident in the artery wall to focal losses of medial muscle cells [25, 29, 36]. Hyalinization, on the other hand, appears to be a replacement of lost arteriolar cells by blood-derived proteinaceous materials in a manner akin to thrombosis, but without participation by important amounts of fibrin or platelets [25, 27–29]. Both processes are correlated with blood pressure and age, but often fail to coexist in the same kidney [16, 20].

This report offers, for the first time, evidence for an association between coronary atherosclerosis and renal arteriolar hyalinization in young people who are free of cardiovascular diseases. Physiological explanations for the association are therefore not ready at hand. Although both hyalinization and atherosclerosis are accelerated by diabetes, the present series of cases was constructed to exclude all known diabetics. It seems fair to ask, therefore, if many of these study subjects may have experienced subclinical degrees of glucose intolerance. A previous report from this series of cases [16] has demonstrated significant correlations between arteriolar hyalinization and both serum cholesterol level and blood glycohemoglobin content. Those findings could suggest the possibility of disorders in the blood lipoprotein patterns and glucose tolerance as factors underlying both hyalinization and atherosclerosis.

The data reported here, together with those previously reported [16], indicate that the finding of hyaline deposits in the renal arterioles may be a useful marker for those young people who are on a course toward coronary heart disease. If such a marker can be verified, then new ways can be devised to study the early stages of coronary artery disease at autopsy. Moreover, the finding of hyaline deposits in the arterioles, seen in renal biopsies, would take on new significance.

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Reprint requests to Richard Tracy, M.D., Department of Pathology, Louisiana State University Medical Center, 1901 Perdido Street, New Orleans, Louisiana 70112, USA.

Appendix 1

Table 2 presents a list of selected variables together with symbols, units of measure, and basic descriptive statistics, including unadjusted and age adjusted correlation coefficients. This information provides all that is necessary to carry out partial and multiple correlations, and multiple regression. These capabilities will be invaluable in comparisons of these data with similar studies in the future.

Appendix 2

Multiple regression. The question of how raised lesions might relate simultaneously to all of the measures of renovasculopathy was approached by multiple regression. After elimination of statistically insignificant terms, these standardized regression equations were obtained:

$$K_c = 0.37A + 0.16\sqrt{Hy} - 0.12Sx \qquad (R^2 = 0.181) \qquad \text{(Eq. 1)}$$

$$K_a = 0.64A + 0.22\sqrt{Hy} + 0.15R_r \qquad (R^2 = 0.304) \qquad \text{(Eq. 2)}$$

Symbols are defined in Table 2, except that here they represent the respective quantities in standardized form. These equations summarize and extend the results of Figures 2 to 4. Equation 1 indicates that hyalinization ($\beta = 0.16$) has about half the strength of age ($\beta = 0.37$) in relation to coronary raised lesions, and is about as strong as the female-male difference ($\beta = -0.12$), whereas fibroplasia has no significant effect (β = not significant and therefore omitted). In relation to aortic raised lesions (Eq. 2), no significant race or sex effect is seen; fibroplasia (0.15 R_r) has about the same strength as hyalinization (0.22 $\sqrt{Hy}$) with effects that are additive and independent of each other.

Appendix 3

Five studies have reported correlation coefficients relating blood pressure to the hyaline and fibroplastic renovasculopathies

Table 2. Characteristics and descriptive statistics for selected variables in 573 autopsies with basal causes of death at ages 25 to 54 years

Variable	Symbol	Units	Number of cases	Mean	SD	Correlation coefficients								
						K_c	K_a	L_c	L_a	R_c	R_r	$\sqrt{Hy}$	A	B	Sx
Dependent variables															
RL Coron.	K_c	% surf.	558	7.8	13.7	—	0.45[a]	0.47[a]	0.05	0.24[a]	0.19[a]	0.30[a]	0.41[a]	−0.08	−0.07
RL Aorta	K_a	% surf.	564	11.5	17.3	0.29[a]	—	0.16[a]	0.06	0.29[a]	0.32[a]	0.32[a]	0.56[a]	−0.06	0.04
FaF Coron.	L_c	% flat surf.	558	7.6	9.8	0.43[a]	0.04	—	0.17[a]	0.19[a]	0.10[b]	0.12[b]	0.23	0.14	0.08
FaF Aorta	L_a	% flat surf.	564	28.8	15.9	0.08	0.11[b]	0.19[a]	—	−0.09	−0.04	−0.12[b]	−0.05	0.16	0.12
Independent variables															
Fibroplasia	R_c	%od	402	8.7	3.0	0.06	0.05	0.09	−0.08	—	0.69[a]	0.24[a]	0.46[a]	0.08	0.16[a]
Fibroplasia	R_r	%od	402	6.4	2.1	0.05	0.15[b]	0.02	−0.02	0.63[a]	—	0.31[a]	0.36[a]	0.11[b]	0.04
Hyaline	$\sqrt{Hy}$	$\sqrt{(N/cm^2)}$	392	1.8	1.5	0.18[a]	0.20[a]	0.06	−0.11[b]	0.13[b]	0.23[a]	—	0.30[a]	−0.14[a]	−0.16[a]
Controlled variables															
Age	A	Years	573	36.2	8.1	—	—	—	—	—	—	—	—	−0.10[b]	0.09[b]
Race	B	100 = B, 0 = W	573	71.2	45.3	−0.04	−0.05	0.17[a]	0.15[a]	0.15[a]	0.16[a]	−0.11[b]	—	—	−0.03
Sex	Sx	100 = F, 0 = M	573	23.9	42.7	−0.12[b]	−0.02	0.06	0.13[a]	0.13[a]	0.00	−0.20[a]	—	−0.02	—

Abbreviations are: R_c and R_r, artrial fibroplasia in the close and remote vessels, respectively; RL, raised lesions; FaF, fatty streaks among flat surfaces; coron., coronary arteries. Unadjusted correlations are in upper triangle, and age-adjusted correlations in lower triangle.

[a] $P < 0.01$

[b] $P < 0.05$ for the difference from zero

separately [3, 4, 8, 20, 21]. Those five coefficients can be pooled by use of Z-transforms to yield correlations with blood pressure of $r = 0.48$ for hyalinization and $r = 0.59$ for fibroplasia as the estimates which combine all existing data. These coefficients can be shown to differ significantly from each other ($P < 0.01$). These provisional findings imply that blood pressure correlates better with arterial intimal fibroplasia than with arteriolar hyalinization. This conclusion has been further strengthened by comparisons between populations. In New Orleans, higher blood pressures in African Americans than in Caucasians were found to accompany greater degrees of fibroplasia but without significant difference in hyalinization [5]. Blood pressure differences among Japan, Guatemala, and USA were paralleled by commensurate differences in fibroplasia, but not of hyalinization [6].

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